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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,946	03/02/2007	Lars-Goran Axelsson	INDEX1140-1	1558
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DLA PIPER US LLP 4365 EXECUTIVE DRIVE SUITE 1100 SAN DIEGO, CA 92121-2133			PITRAK, JENNIFER S	
			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/582,946	Applicant(s) AXELSSON ET AL.	
	Examiner Jennifer Pitrak	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) 7, 8 and 28-31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 9-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>08/29/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-27) drawn to an siRNA molecule directed to a p65 subunit of NF-kappa-B and expression vectors encoding the siRNA molecule, and complementary sequences: SEQ ID NO: 5 and SEQ ID NO: 9 in the reply filed on 10/15/07 is acknowledged.

Claims 7, 8, and 28-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/15/07.

Applicants further elected, without traverse, the complementary SEQ ID NOs: 5 and 9 for examination in the reply filed on 10/15/07.

Claims 1-6 and 9-27 are currently being examined on the merits.

Claim Objections

Claim 25 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 25 does not further limit the siRNA molecule of claim 1, which is referenced in claim 22, because the limitations of claim 25 are already present in claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, and 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4 and 5 recite the limitation "said linker molecule". There is insufficient antecedent basis for this limitation in the claims. Claims 13-16 recite the limitation "strand". There is insufficient antecedent basis for this limitation in the claims.

Claims 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims read "antisense and/or sense" but then further limit only the antisense, rendering the claims indefinite as to which strand or region is to contain the referenced phosphorothioate internucleotide linkages.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

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Claims 1-4, 9-14, and 21, 22, and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Khvorova, *et al.* (US 2007/0031844, filed under US provisional application 60/502,050 on 09/10/03).

The claims are directed to an siRNA molecule targeting the p65 subunit of NF-kappa-B comprising sense and antisense strands, wherein the sense strand comprises SEQ ID NO: 9 (claim 2) and the antisense strand comprises SEQ ID NO: 5 (claim 1) or substantially homologous sequences thereof. The claims are to the siRNA molecule wherein the sense and antisense regions are linked via a polynucleotide (claims 3 and 4). The claims are further to the siRNA molecule of claim 1, wherein the sense and antisense strands comprise 1-5 natural or modified 3'-terminal overhanging nucleotides (claims 9, 10, and 21) and wherein the antisense 3'-terminal overhanging nucleotides are complementary to RNA encoding p65 (claim 11). Claims 12-14 are to the siRNA molecule of claim 1 further comprising at least one 2'-O-methyl modified pyrimidine in the sense strand (claim 12), a 5'- and/or 3'-end cap on the sense strand (claim 13), and at least one 2'-deoxy-2'-fluoro modified pyrimidine in the antisense strand (claim 14). Claims 21, 22, and 25-27 are to expression vectors comprising the siRNA targeting p65.

Khvorova, *et al.* disclose SEQ ID NO: 430561, which is complementary to 18 of 21 nucleotides of SEQ ID NO: 5 and which is 17 of 21 nucleotides of SEQ ID NO: 9 as shown below.

(Khvorova, <i>et al.</i>) SEQ ID NO: 430561	5' -GGACAU AUGAGACCUUCAA- 3'
SEQ ID NO: 5	3' -TTCCUGGAUACUCUGGAAGUU- 5'
SEQ ID NO: 9	5' -GGACCUAUGAGACCUUCAATT- 3'

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SEQ ID NO: 430561 of Khvorova, *et al.* is one strand of an siRNA, which is substantially homologous to the siRNA comprised of SEQ ID NOs: 5 and 9 of the instant application.

Khvorova, *et al.* disclose that the siRNAs of their invention can be comprised of two separate strands or can be covalently linked by a polynucleotide sequence and that the strands can have overhanging unpaired bases at the 5' or 3' ends (p.5, paragraph 0105). The authors provide the example of an siRNA molecule wherein two 21-nucleotide strands are complementary over the first 19 nucleotides and that the remaining bases (2 bases for each strand) exist as overhangs (p.7, paragraph 0118). The two nucleotide overhangs are most often deoxythymidines (see Khvorova, p.18, paragraph 0266), in which case SEQ ID NO: 430561 would be complementary to the RNA encoding the p65 subunit of NF-kappa-B (see SEQ ID NO: 1 in Table 1 of the instant application on p.14). Khvorova, *et al.* further disclose that siRNAs may contain 2'-O-methyl- or 2'-deoxy-2'-fluoro-modified nucleotides, including pyrimidines (p.7, [0120-0121]), and that the sense strand may comprise a terminal cap at its 3' end (as disclosed in claim 8 of U.S. Patent Application 10/613,077 incorporated by reference in Khvorova, *et al.*, p.18, [0268]). The inventors also teach that the siRNAs of their invention could be applied *in vivo* or *in vitro* by "synthesizing equivalent DNA sequences (either as two separate, complementary strands, or as hairpin molecules) instead of siRNA sequences and introducing them into cells through vectors," including traditional expression vectors (p.19, paragraph 0277). Thus, Khvorova, *et al.* anticipate all of the instant claims 1-4, 9-14, and 21, 22, and 25-27.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 6, 9-14, and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khvorova, *et al.* (2007, US 2007/0031844, filed 11/14/03).

Claims 1-4, 9-14, and 21, 22, and 25-27 are described in the previous rejection. Claim 6 is to the siRNA molecule of claim 1 described above, wherein the sense region comprises SEQ ID NO: 9 and the antisense region comprises SEQ ID NO: 5. Claims 23 and 24 are to a mammalian cell, specifically a human cell, comprising the expression vector of claim 22 as described above in the 102(a) rejection.

Khvorova, *et al.* teach an siRNA comprising SEQ ID NO: 430561 with 2-nucleotide dTdT overhangs as described above (paragraph [0266]), which comprises 20 of 21 nucleotides of SEQ ID NO: 9. The inventors also teach that within the duplex region of siRNAs, the two strands can be completely or substantially complementary, "for example, a polynucleotide strand having 21 nucleotide units can base pair with another polynucleotide of 21 nucleotide units, yet only 19 bases on each strand are complementary or substantially complementary, such that the "duplex region" has 19 base pairs. The remaining bases may, for example, exist as 5' and 3' overhangs. Further, within the duplex region, 100% complementarity is not required; substantial complementarity is allowable within a duplex region. Substantial complementarity

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refers to 79% or greater complementarity. For example, a mismatch in a duplex region consisting of 19 base pairs results in 94.7% complementarity, rendering the duplex region substantially complementary," (p.7, [0118]). Khvorova, *et al.* do not explicitly teach siRNAs comprising SEQ ID NO: 5 and SEQ ID NO: 9.

It would have been obvious to make the siRNA molecule of the instant claim 6, comprising SEQ ID NO: 5 and SEQ ID NO: 9 because Khvorova, *et al.* teach that siRNAs with a range of complementarity including 100% complementarity is useful for siRNA function and the inventors teach SEQ ID NO: 430561 with 2 overhanging dT's, which is only one-nucleotide difference from the instant SEQ ID NO: 9. Thus, claim 6 would have been obvious at the time of the instant application.

Khvorova, *et al.* teach the expression vector as described above and they teach introduction of such vectors into cells (p.19, [0277]) and transfection of HeLa cells with siRNAs (p.32, [0335]). Khvorova, *et al.* do not specifically teach a human or mammalian cell comprising an expression vector containing the SEQ ID NOs: 5 and 9 of the instant claims 23 and 24.

It would have been obvious to make a human cell comprising the claimed vector because Khvorova suggest the use of such vectors to deliver siRNAs in lieu of direct transfection of siRNAs to cells. One would expect the expression vector to generate siRNAs because the purpose of an expression vector is to express a gene or RNA of interest in a cell. Thus, claims 23 and 24 would have been obvious at the time of the present application.

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Claims 1-6 and 9-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khvorova, *et al.*, as applied to claims 1-4, 6, 9-14, and 21-27 above, and further in view of Fosnaugh, *et al.* (US 2003/0143732, filed 08/20/02).

Claims 1-4, 6, 9-14, and 21-27 are described above. Claim 5 is to the siRNA molecule of claim 1 further comprising a non-nucleotide linker molecule. Claims 15 and 16 are to the siRNA molecule of claim 1, wherein the antisense strand comprises 1-5 phosphorothioate internucleotide linkages at the 3'-end (claim 15) or 5'-end (claim 16). Claims 17-20 are to the siRNA of claim 9, comprising 3'-terminal overhangs on both strands, wherein the terminal overhangs comprise sugar-, base-, or backbone-modified ribo- or deoxyribo-nucleotides, one or more universal base ribonucleotides, or one or more acyclic nucleotides.

Khvorova, *et al.* teach the siRNAs comprising a polynucleotide linker as described above for claim 4. The inventors do not teach non-nucleotide linkers.

Khvorova, *et al.* teach the siRNAs comprising 3'-terminal overhangs as described above. The inventors further teach the incorporation of modified nucleotides into siRNA molecules including sugar-, base-, and backbone-modified ribo- and deoxyribonucleotides, universal base ribonucleotides, and acyclic nucleotides (p.7 paragraphs [0120]-[0122]). Khvorova, *et al.* do not specifically teach the specific numbers and locations (3'-terminal) of these modifications within the siRNA molecule.

Fosnaugh *et al.*, teach siRNAs directed to ADORA1 and that the sense and antisense regions of the siRNA can be covalently connected via a non-nucleotide linker (p.3, paragraph [0015]). Fosnaugh, *et al.* further teach that the siRNA molecule can comprise a phosphorothioate internucleotide linkage at the 3'-end of the antisense region and about 1-5

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phosphorothioate internucleotide linkages at the 5'-end of the antisense region (p.3, paragraph [0019]). The inventors teach that the 3'-terminal overhangs of an siRNA molecule can comprise ribo- or deoxyribonucleotides that are chemically modified at a sugar, base, or backbone and that the 3'-terminal overhangs can also comprise one or more universal base ribonucleotides or acyclic nucleotides (paragraph [0020]).

It would have been obvious to make the siRNA as taught by Khvorova, *et al.*, further comprising non-nucleotide linkers and sugar, base, and backbone modifications of the 3'-terminal overhangs, as taught by Fosnaugh, *et al.* One would have been motivated to make siRNAs comprising non-nucleotide linkers because Fosnaugh, *et al.* teach that such linkers can provide a convenient experimental design (see p.17, paragraph [0147]). One would have been motivated to make siRNA molecules comprising the modifications described above because Fosnaugh, *et al.* teach that such modifications can improve the efficacy and nuclease resistance of siRNAs (pp.4-5, paragraph [0034]). One would expect the siRNAs with the non-nucleotide linkages and the modified nucleotides to be effective because such siRNAs were effective for inhibiting ADORA1 expression, as described by Fosnaugh, *et al.* Thus, claims 1-6 and 9-27 would have been obvious to one skilled in the art at the time of the instant application.


Closing

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Pitrak whose telephone number is 571-270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak
Patent Examiner
Art Unit 1635


Examiner, Art Unit 1635